residue, and the mixture was extracted with ether. The combined organic solutions were washed with water followed by saturated brine and were dried over anhydrous magnesium sulfate. The crude pale yellow oil obtained on evaporation of the solvent at reduced pressure was chromatographed on 29 g of Merck acid-washed alumina. The fraction eluted with 50% ether in pentane was submitted to short-path distillation at 122–123° (17 mm) to give 0.334 g (67% over-all yield from the bromo diene) of a colorless liquid, n^{25}D 1.4680, λ_{max}^{film} 3.00 (OH), 3.25, 6.07, and 11.22 (C=CH$_2$), 12.2 (C=CH), and 9.55 μ (CO). The vapor phase chromatogram on a 7.5-ft Carbowax column at 140° showed a major component comprising 94% of the total area at retention time 20.3 min. A shoulder on this peak with retention time 21.7 min amounted to about 2% of the area and is tentatively considered to correspond to the *cis* isomer. Small "impurity" peaks were found with retention times of 11.6 and 15–19 min. The nmr spectrum showed absorption for 3 protons as a singlet at δ 1.64 ppm (CH$_3$ at C-3), 3 protons as a singlet at 1.71 (CH$_3$ at C-7), 7 protons appearing as a "singlet" at 2.06 and a multiplet centered at 2.17 (C-2, -5, and -6 methylenes and OH), 2 protons as a triplet (J = 6.5 cps) centered at 3.55 (C-1 methylene), 2 protons as a "singlet" at 4.65 (C-8 methylene), and 1 proton as a broad triplet (J = 6 cps) centered at 5.18 (C-4 proton).

An analytical specimen was secured by preparative vapor phase chromatography as described above at 150°. The major component, retention time of about 70 min, was obtained as a colorless liquid, n^{24}D 1.4685.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 78.0; H, 11.8.

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A Stereoselective Synthesis of Racemic Andrographolide Lactone

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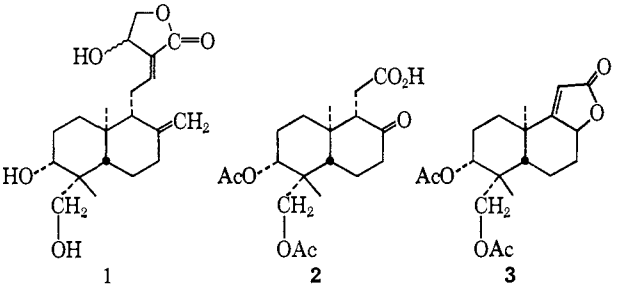
Contribution from the Department of Chemistry, University of Georgia, Athens, Georgia 30601. *Received December 15, 1967*

Abstract: This paper reports a ten-step stereoselective synthesis of the racemic α,β-unsaturated lactone **3**, which has been obtained previously in optically active form by degradation of triacetylandrographolide. The stereochemistry of ring fusion and the relative configurations of the substituents at C-4 in the crucial bicyclic intermediate **22** were established by chemical reactions and analysis of the nmr spectra of compounds **18b** and **19**. Methylation of **15** obtained by selective ketalization of **6** afforded **16** in 63% yield. Reduction of the latter with $NaBH_4$ afforded **17** which was reduced with $LiAlH_4$ to the diol **28**. Acetylation of **28** followed by deketalization gave the keto diacetate **30** which on hydrogenation and subsequent oxidation afforded the *trans*-decalin **22**. The same compound was obtained by the sequence **17** → **19** → **22**. Treatment of **22** with lithium ethoxyacetylide gave an ethynylcarbinol **32** which was rearranged in acid to the α,β-unsaturated ester **33**. Oxidation of **33** with selenium dioxide in acetic acid gave lactone **34**.

Andrographolide, the main bitter principle of *Andrographis paniculata* Nees (rice bitters), was first isolated by Gorter[1] and characterized as a trihydroxy lactone. Subsequent work,[2-8] particularly by Cava and his collaborators,[6,8] established the structure and stereochemistry of this interesting molecule as **1**. As a possible intermediate for the total synthesis of andrographolide we set out to synthesize the racemic α,β-unsaturated lactone **3** which has been obtained in the optically active form by ozonolysis of triacetylandrographolide to the diacetoxyketo acid **2** followed by refluxing with acetyl chloride.[8] The stereospecific synthesis of this degradation product confirms not only the structure of the α,β-unsaturated lactone **3** but also the structure and relative stereochemistry of rings A and B of andrographolide (**1**).



5-Carbomethoxy-9α-methyl-1,6-dioxo-$\Delta^{5(10)}$-octalin (**6**) was used as a convenient source of the bicyclic ring system. The condensation of carbomethoxymethyl vinyl ketone[9-11] (**4**) with 2-methylcyclohexane-1,3-dione[12] (**5**) in the presence of anhydrous potassium fluoride[13-15] in dry methanol gave the ketone **6** in one step in 30–50% yield. When benzene or toluene[13] was

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(2) R. Schwyzer, H. G. Biswas, and P. Karrer, *Helv. Chim. Acta*, **34**, 652 (1952), and references cited therein.
(3) R. J. C. Kleipool and D. G. F. R. Kostermans, *Rec. Trav. Chim.*, **70**, 1085 (1951); R. J. C. Kleipool, *Nature*, **169**, 33 (1952).
(4) D. Chakravarti and R. N. Chakravarti, *J. Chem. Soc.*, 1697 (1952).
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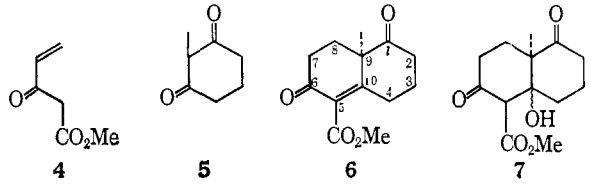
(7) M. P. Cava, W. R. Chan, L. J. Haynes, and L. F. Johnson, *Tetrahedron*, **18**, 397 (1962); M. P. Cava, B. Weinstein, W. R. Chan, L. J. Haynes, and L. F. Johnson, *Chem. Ind.* (London), 167 (1963).
(8) M. P. Cava, W. R. Chan, R. P. Stein, and C. R. Willis, *Tetrahedron*, **21**, 2619 (1965).
(9) E. Wenkert, A. Afonso, J. B-son Bredenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964).
(10) R. Hohenlohe-Oehlngen, *Monatsh.*, **93**, 576 (1962).
(11) I. N. Nazarov and S. I. Zavyalov, *Zh. Obshch. Khim.*, **23**, 1703 (1953); *J. Gen. Chem. USSR*, **23**, 1793 (1953).
(12) Columbia Organic Chemicals Co., Inc., Columbia, S. C.
(13) Y. Kitahara, A. Yoshikoshi, and S. Oida, *Tetrahedron Letters*, No. **26**, 1763 (1964).

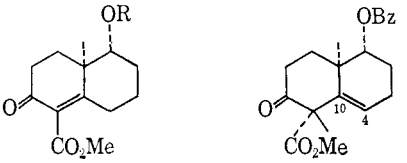
used as the solvent, the 10-hydroxy ketone **7** was obtained. The desired keto enone ester **6** was readily obtained by dehydration of **7** in refluxing benzene in the presence of a trace of *p*-toluenesulfonic acid. When sodium methoxide was used as the base and methanol as the solvent in the condensation, the hydroxy ketone **7** was again obtained.



4 **5** **6** **7**

To protect the 1-keto group in the reactions that were to follow, several procedures were attempted. Selective reduction[16] of the keto group at C-1 in **6** was realized with sodium borohydride in 50% yield and the benzoate **9** was prepared in 60% yield by treatment of the alcohol **8** with benzoyl chloride–pyridine. An attempt to prepare the tetrahydropyranyl ether **10** of the alcohol was unsuccessful.[17]

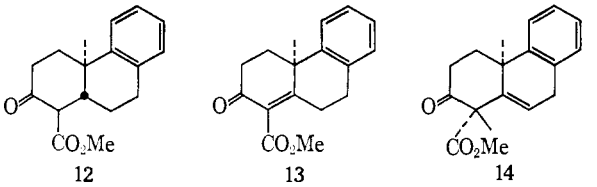
Stereospecific methylation of the benzoate **9** with methyl iodide and potassium *t*-butoxide proceeded without incident[18] to give the 4β-methyl ketone **11** in 75% yield, the product exhibiting C-methyl singlets in the nmr at τ 8.70 and 8.57. Wenkert[9] has shown that methylations of decalone systems such as **12** give a mixture of epimers in which the α epimer (*cis* to C-10 methyl) predominates (2.4:1). However, when an α,β-unsaturated β′-keto ester such as **13** was methylated,[9] the only isolable product **14** resulted from exclusive β attack (*trans* to C-10 methyl group).



8, R = H
9, R = Bz
10, R = THP

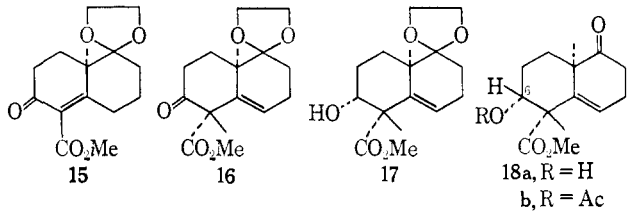
11

With this as a precedent it seemed reasonable to assume that the methylation product had the stereochemistry depicted in **11**.



12 **13** **14**

Since attempts to saturate the 4,10 double bond of **11** by catalytic hydrogenation failed, the use of the ethylene ketal as a protecting group for the C-1 carbonyl group of **6** was explored. Initial experiments using *p*-toluenesulfonic acid monohydrate resulted in inseparable mixtures of the mono- and diketal derivatives. It was found, however, that using anhydrous *p*-toluenesulfonic acid[19] in place of the hydrate and limiting the reaction time to 2 hr increased the selectivity of the reaction. Thus the monoketal **15** was prepared in 84% yield. Stereospecific methylation of the ketal in benzene using potassium *t*-butoxide as the base afforded the desired methylated product **16** in 63% yield. (For proof of the indicated stereochemistry see below.) Since catalytic hydrogenation of **16** also proved unfruitful, we decided to postpone hydrogenation to a later stage.



15 **16** **17** **18a**, R = H; **b**, R = Ac

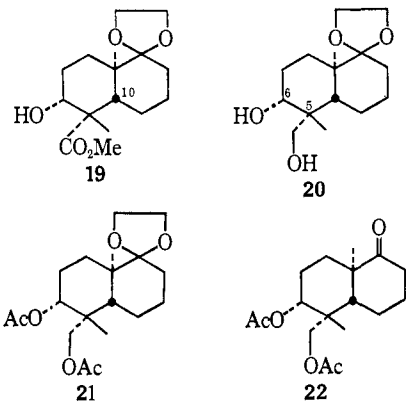
Stereospecific reduction of the methylated ketone **16** with sodium borohydride in dry or aqueous methanol afforded the unsaturated alcohol **17** in 90% yield. The newly introduced hydroxyl group was assigned the more stable α configuration on the basis of the observation of Graham and McQuillin.[20] The assignment is also supported by the nmr spectrum of 6α-acetoxy-5α-carbomethoxy-5β,9α-dimethyl-1-oxo-$\Delta^{4(10)}$-octalin (**18b**) obtained by deketalizing **17** and acetylating the product. The splitting of the C-6 hydrogen into four lines (1 H) of equal intensity at τ 5.54 wth $J_{AX} + J_{BX} = 16$ cps requires the C-6 hydrogen to be axial.

Reduction of the double bond of **17** was effected in methanol in 7 days with 10% palladized charcoal[21] at room temperature. Although the nmr spectrum ($CDCl_3$) of a once crystallized sample (mp 120–127°) showed only two sharp methyl signals at τ 9.0 and 8.6 the product had to be crystallized repeatedly before a pure, sharp-melting specimen could be obtained in 33% yield. Tlc examination of the mother liquors revealed that the desired *trans*-2-decalol **19** was the main component contaminated with three other compounds possessing close R_f values. The presence of a sharp 3 H signal in the nmr[22] spectrum (CCl_4) of pure **19** at τ 9.2 indicated the *cis*-1,3-diaxial relationship of the carbomethoxyl and the angular methyl groups and also confirmed that the hydrogenation had occurred from the less hindered β side for which there are ample precedents.[23]

Lithium aluminum hydride reduction of the hydroxy ester **19** in tetrahydrofuran–ether gave the diol **20**[24] in 80% yield. Treatment of **20** with acetic anhydride–

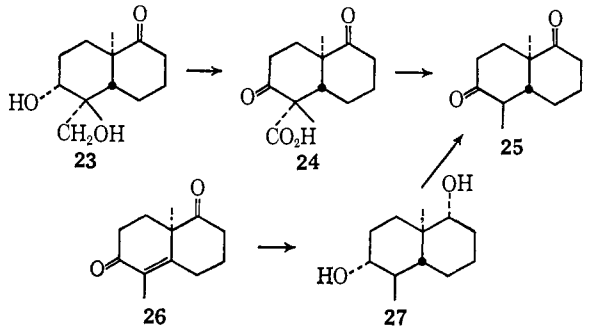
(14) M. Igarashi, H. Midorikawa, and S. Aoyama, *Sci. Paper Inst. Phys. Chem. Res.* (Tokyo), **52**, 151 (1958).
(15) L. Rand, J. V. Swisher, and C. J. Cronin, *J. Org. Chem.*, **27**, 3505 (1962).
(16) J. K. Noriymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).
(17) A. C. Ott, M. F. Murray, and R. F. Pederson, *J. Am. Chem. Soc.*, **74**, 1239 (1952).
(18) T. A. Spencer, T. D. Weaver, and W. J. Gireco, Jr., *J. Org. Chem.*, 30, 3333 (1965).
(19) E. J. Corey, M. Ohno, R. B. Mitra, and G. A. Vatakencherry, *J. Am. Chem. Soc.*, **86**, 478 (1964).
(20) C. L. Graham and F. J. McQuillin, *J. Chem. Soc.*, 4634 (1963).
(21) Prepared by the method described in Vogel: A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green, and Co., London, 1959, p 950.
(22) A. H. Kapadi and S. Dev, *Tetrahedron Letters*, 1171 (1964).
(23) (a) F. Sondheimer and D. Elad, *J. Am. Chem. Soc.*, **80**, 1967 (1958); (b) J. D. Cocker and T. G. Halsall, *J. Chem. Soc.*, 3441 (1957); (c) G. Stork and J. W. Schulenberg, *J. Am. Chem. Soc.*, **78**, 1250 (1956).
(24) The non-*trans*-diaxial relationship of the C-5 hydroxymethyl and C-6 hydroxyl groups was confirmed by the ease with which a compound related to 20 forms an acetylidene derivative on reaction with acetaldehyde in the presence of fused zinc chloride (unpublished observation, S. W. Pelletier and S. Prabhakar).

pyridine afforded the ketal diacetate **21** in 80% yield. The yield in the step **19** → **21** could be improved to 92% if the crude diol **20** was acetylated and the product directly crystallized (see Experimental Section). Deketalization of **21** with *p*-toluenesulfonic acid in aqueous acetone gave the keto diacetate **22** (after reacetylation) in 92% yield.

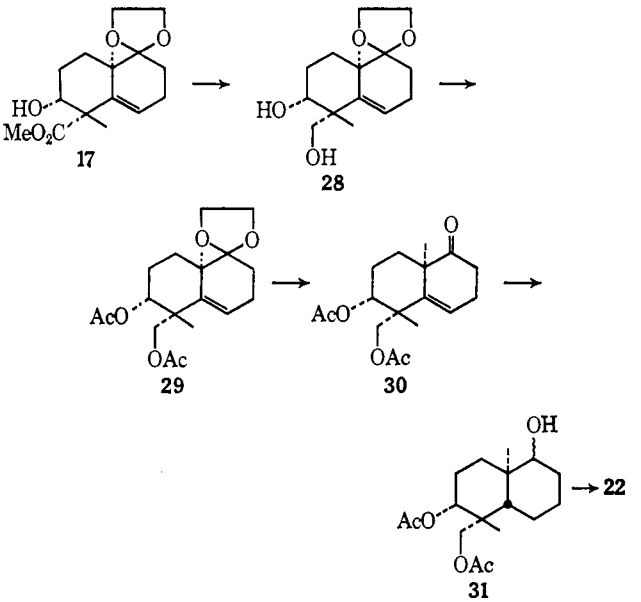


Stereochemistry of Rings A/B

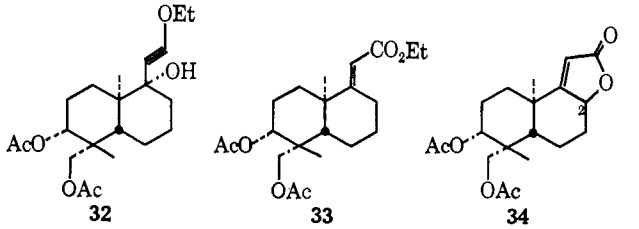
Although the nmr data of **19** fully supported the *trans*-A/B fusion of its rings and the compounds derived therefrom, it was thought worthwhile to provide independent chemical evidence for the C-10 stereochemistry. With this end in view, **22** was hydrolyzed with aqueous alcoholic alkali to the keto diol **23**, mp 121–123°, ν_{max} 3390 and 1704 cm^{-1}. Oxidation of **23** with the Jones' reagent[25] at room temperature gave the diketo acid **24** which without purification was decarboxylated by refluxing in a mixture of glacial acetic acid and concentrated hydrochloric acid to the nor diketone **25**. Reduction[26] of the known 5,9-dimethyl-1,6-dioxo-$\Delta^{5(10)}$-octalin[13] (**26**), obtained from condensation of ethyl vinyl ketone with **5**, with lithium in liquid ammonia followed by reductive work-up (EtOH) gave the 1,6-dihydroxy-*trans*-decalin (**27**) which without purification was oxidized with an excess of the Jones' reagent[25] at 0° to the known 5β,9α-dimethyl-1,6-dioxo-*trans*-decalin.[27] The infrared spectrum of this compound was superimposable on that of the nor diketone **25** and there was no depression in the melting points of the samples. This sequence of reactions unequivocally demonstrates the *trans*-A/B fusion in **19** and its derivatives.



The rather low yield obtained in the reduction of **17** prompted us to investigate other catalysts and solvents. On one occasion reduction of **17** in dry ethyl acetate afforded the pure *trans*-decalol **19** in 82% yield. At other times the reduction of the double bond could not be effected at all. Though the preparation of the palladium catalyst was carefully standardized, the activity of the catalyst varied widely. Attempted reduction of **17** or its acetate with Adams' catalyst in glacial acetic acid failed. Because of the lack of reproducibility of the reduction in one case and complete failure in the other, a modified route from **17** to **22** was developed. Reduction of **17** with lithium aluminum hydride to **28** followed by acetylation gave the unsaturated ketal diacetate **29**. Deketalization with *p*-toluenesulfonic acid in aqueous acetone afforded the keto diacetate **30**. Reduction of **30** with PtO_2–HOAc was rapid and gave the *trans*-1-decalol **31** which on oxidation with the Jones' reagent[25] gave **22**. The over-all yield from **17** to **22** by this route was 66% of **22** melting at 105–110°. Recrystallization afforded pure **22** indistinguishable from the sample prepared by the other route. This sequence when applied to **16** gave a reduced over-all yield (48%).



The acetic acid side chain was attached to the bicyclic ring system by treatment of ketone **22** with lithium ethoxyacetylide.[28,29] The crude acetylide **32**, ν_{max} (CCl_4) 3560, 2268, 1742, and 1235 cm^{-1}, was immediately treated with 5% sulfuric acid to afford the α,β-unsaturated ester **33**.[28,29] Allylic oxidation of **33** with selenium dioxide[28,29] in glacial acetic acid provided an α,β-unsaturated lactone **34**.



(25) K. Bowden, I. M.Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(26) A. J. Birch, E. Pride, and H. Smith, *ibid.*, 4688 (1958).
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(28) N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron Letters*, 310 (1961).
(29) N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **23**, 509 (1967).

The β configuration[29] of the C-2 oxygen is assigned on the basis of the principle of steric approach of the reagent from the less hindered side. The infrared (CCl_4) and mass spectra of the synthetic lactone **34** were identical in all respects with those of the naturally derived sample.[8] In addition identical behavior was observed on thin layer alumina chromatoplates in the systems ethyl acetate–ether (1:4) and methyl alcohol–benzene (1:24) using iodine vapor as the developing agent.

Thus the stereospecific synthesis of the racemic form of Cava's α,β-unsaturated lactone **34** confirms the assignment for the structure and stereochemistry of the bicyclic ring system of andrographolide in addition to providing a possible route in the total synthesis of andrographolide and compounds such as iresin.

Experimental Section

General Procedures. Melting points are corrected and were taken on a hot stage equipped with a microscope and polarizer. Finely powdered samples were placed on the stage 15° below the melting point, and the temperature was raised at a rate of about 4°/min. Ultraviolet spectra were determined in 95% ethanol on a Perkin-Elmer Model 202 spectrophotometer and infrared spectra on Perkin-Elmer Model 137 or 237 spectrophotometers. Infrared spectra are in Nujol unless otherwise indicated. Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 spectrometer in carbon tetrachloride, unless otherwise stated,[30] with tetramethylsilane as an internal standard. The removal of solvents *in vacuo* was accomplished with a Craig-type rotating flash evaporator at 15–20 mm, and with the water bath usually at 35–50°.

β-Ethoxypropionyl Chloride ($C_2H_5OCH_2CH_2COCl$). Thionyl chloride (1 kg) was cooled to 0° and treated dropwise (4 hr) with 850 g of β-ethoxypropionic acid, stirring vigorously throughout the addition. The reaction mixture was stirred overnight at room temperature and distilled at reduced pressure: 65–67° (31 mm). The distillation provided 895 g of β-ethoxypropionyl chloride.

Methyl 3-Oxo-4-pentenoate[9] ($CH_2{=}CHC{=}OCH_2CO_2CH_3$) **(Carbomethoxymethyl Vinyl Ketone).** A solution of 219 g of β-ethoxypropionyl chloride in 200 ml of ether was added slowly to an ice-cold slurry of methyl sodioacetoacetate (prepared from 175 g of methyl acetoacetate and 37 g of sodium, in 1 l. of ether). The suspension was stirred at room temperature for 18 hr. Gaseous ammonia was passed through the cold solution, keeping the temperature between 5 and 10° until the solution cleared. The clear yellow solution was immediately washed with water and then with cold 10% hydrochloric acid and then again with water. The ether was evaporated *in vacuo*, and the oil that remained was vacuum distilled, collecting 65 g of β-ethoxypropionylacetic acid, bp 82–84° (1 mm). A comparable yield of the product was also obtained with sodium hydride (58% dispersion, 65 g) as the condensing agent.

A suspension of 85 mg of *p*-toluenesulfonic acid in 6.0 g of methyl β-ethoxypropionylacetate ($C_2H_5OCH_2CH_2C{=}OCH_2CO_2CH_3$) was heated on an oil bath at 130° and refluxed for 5 min under vacuum (75–100 mm) and then vacuum distilled, bp 63–65° (19 mm), providing 3.2 g of methyl 3-oxo-4-pentenoate. Sometimes it was found necessary to carry out the reaction with more than a catalytic amount of *p*-toluenesulfonic acid (0.70 g of *p*-TsOH for 10 g of methyl β-ethoxypropionylacetate).

5-Carbomethoxy-1,6-dioxo-9α-methyl-$\Delta^{5(10)}$-octalin (6). A solution of 9.50 g of methyl 3-oxo-4-pentenoate[9] in 10 ml of dry methanol was added dropwise to a solution of 7.50 g of 2-methylcyclohexane-1,3-dione and 8.00 g of anhydrous potassium fluoride[13–15] in 250 ml of dry methanol. The solution was stirred for 15 hr at room temperature, and the solvent was evaporated *in vacuo*. The residue was extracted with ether and washed with 10% aqueous sodium carbonate solution until colorless washings were obtained. The ethereal layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* leaving 11.40 g of yellow oil. When a sample of oil was seeded with a crystal of the enone **6**, the product gradually solidified. Recrystallization from ether gave crystalline **6**, mp 70–71°; ν_{max} 1733 (CO_2CH_3), 1704 (ketone), 1672 (α,β-unsaturated ketone), and 1616 cm^{-1} (C=C); λ_{max} 250 mμ (10,000); τ 8.53 (3 H singlet, CCH_3) and 6.24 (3 H singlet, CO_2CH_3).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.20; H, 6.82.

5-Carbomethoxy-1α-hydroxy-9α-methyl-6-oxo-$\Delta^{5(10)}$-octalin (8).[16] A solution of 8.0 g of the keto enone **6** in 150 ml of absolute ethanol was cooled to 0° in an ice–salt bath. A solution of 687 mg of sodium borohydride in 150 ml of ethanol was added dropwise and allowed to stand at 0° for 1 hr. The excess sodium borohydride was neutralized with 5 ml of glacial acetic acid and the solvent removed *in vacuo*. The residue was dissolved in water and the solution extracted with ether. The ether solution was washed well with water until the aqueous washings were neutral and then was dried over sodium sulfate and evaporated *in vacuo* to give an oily residue which solidified rapidly. The product was crystallized from ethyl acetate–hexane (1:1) to afford 4.88 g of crystalline alcohol **8**, mp 159–161°; ν_{max} 3510 (OH), 1720 (ester), 1675 (ketone), and 1615 cm^{-1} (C=C); λ_{max} 248 (11,300); τ 8.77 (3 H singlet, CCH_3) and 6.20 (3 H singlet, CO_2CH_3).

Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.28; H, 7.45.

Benzoate of 5-Carbomethoxy-1α-hydroxy-9α-methyl-6-oxo-$\Delta^{5(10)}$-octalin (9). A solution of 3.02 g of alcohol **8** in 25 ml of freshly distilled pyridine was treated with benzoyl chloride at 0°. The mixture was allowed to stand overnight and the excess benzoyl chloride was hydrolyzed by adding 25 ml of water and storing the mixture in the refrigerator 48 hr. The solution was concentrated *in vacuo* and benzene–ether solution (1:1) was used to extract the residue. The extract was washed first with 10% hydrochloric acid and then with 10% sodium bicarbonate. The solvent was then evaporated *in vacuo* to yield 2.60 g of the solid benzoate **9**. Recrystallization of the product from methanol gave a white crystalline solid, mp 160–161°; ν_{max} 1740, 1720, 1685, and 1630 cm^{-1}; λ_{max} 237 mμ (23,200); τ 2.2–3.1 (multiplets, aromatic hydrogens), 8.53 (3 H singlet, CCH_3), and 6.18 (3 H singlet, CO_2CH_3).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.50, 70.72; H, 6.59, 6.41.

Benzoate of 5α-Carbomethoxy-5β,9α-dimethyl-1α-hydroxy-6-oxo-$\Delta^{4(10)}$-octalin (11).[9] Potassium (97 mg) was dissolved in 3.2 ml of refluxing *t*-butyl alcohol, which was then removed *in vacuo* and flashed with benzene several times. Benzene (5 ml) was added to the residue followed by a solution of 268 mg of benzoate **9** in 3 ml of benzene with stirring for 5 min under nitrogen. The golden orange solution was cooled and then treated with 0.45 ml of freshly distilled methyl iodide. After stirring for 1 hr solid material began to separate and 25 ml more of dry benzene was added. The reaction mixture was then stirred 4 hr more at room temperature. The benzene solution was treated carefully with 20 ml of water and then washed with water until the washings were neutral. After drying the solution over sodium sulfate, the benzene was evaporated *in vacuo* to afford 206 mg of crude product which was readily purified by chromatography in benzene over 20 g of Florisil. Elution with methylene chloride gave 152 mg of colorless oil: ν_{max} (CCl_4) 1724, 1645, and 1590 cm^{-1}; τ 8.70 (3 H singlet, CCH_3), 8.57 (3 H singlet, CCH_3), 6.30 (3 H singlet, CO_2CH_3), 4.36 (1 H triplet, vinyl proton), and 5.03 (1 H triplet, $CHOCOC_6H_5$).

Attempted Preparation of Tetrahydropyranyl Ether of 5-Carbomethoxy-1α-hydroxy-9α-methyl-6-oxo-$\Delta^{5(10)}$-octalin (10).[17] A solution of 203 mg of hydroxy enone **8** in 5 ml of 3,4-dihydropyran was treated with three drops of hydrochloric acid–dihydropyran (two drops of concentrated HCl in 5 ml of DHP) and let stand for 18 hr. The reaction mixture was diluted with ether, washed with sodium bicarbonate, dried, and evaporated *in vacuo* leaving 210 mg of colorless oil, ν_{max} (neat) 3470, 1724, and 1630 cm^{-1}.

5-Carbomethoxy-1,1-ethylenedioxy-6-oxo-9α-methyl-$\Delta^{5(10)}$-octalin (15).[19] A mixture of 23.7 g of keto enone **6**, 350 ml of dry benzene, and 60 ml of freshly distilled ethylene glycol (dried over K_2CO_3) was refluxed for 1 hr while water was removed as a benzene–water azeotrope with a Bidwell-Sterling trap. Anhydrous *p*-toluenesulfonic acid (180 mg) was added and refluxing continued for 2 hr. The cooled benzene solution was washed with aqueous 5% potassium bicarbonate, then with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residual light yellow oil was crystallized from ether–hexane to give 16.128 g of the ethylene ketal, mp 118–121°. The mother liquor was taken to dryness (15.62 g) and chromatographed over silicic acid (120 g). Elution with ether–hexane (4:1) and evaporation of the first 600 ml of the eluate gave a white residue which upon crystallization

(30) The 100-MHz nmr spectra of compounds **18b** and **21** were taken in deuteriochloroform with a Varian HA-100 spectrometer. The 60-MHz spectra of compounds **8**, **9**, **12**, and **18a** were determined in deuteriochloroform on a Varian A-60 spectrometer.

from ether–hexane furnished an additional 7.41 g of the ketal **15**, mp 119–122°. An analytical sample crystallized from the same solvent pair melted at 120–122°; ν_{max} 1739 (ester), 1672 (enone), and 1618 cm^{-1} (conjugated C=C); λ_{max} 247 mμ (10,200); τ 8.59 (3 H singlet, CCH_3), 6.15 (3 H singlet, CO_2CH_3), and 5.98 (4 H singlet, OCH_2CH_2O).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.41; H, 7.25.

5α-Carbomethoxy-5β,9α-dimethyl-1,1-ethylenedioxy-6-oxo-Δ$^{4(10)}$-octalin (16). Method A. A solution of 3.50 g of the above ethylene ketal dissolved in 10 ml of dry benzene was treated with 3.84 g of commercial potassium *t*-butoxide. The solution was stirred under nitrogen at room temperature for 2 hr and refluxed for 15 min. The ice-cooled reaction mixture was then treated with 10 ml of methyl iodide, stirred at room temperature overnight, and refluxed for 2 hr the next morning. The cooled solution was washed with water until neutral and the solvent evaporated *in vacuo* to yield a colorless oil which solidified (1.81 g) from ether–hexane (2:1). The mother liquors were evaporated *in vacuo* and chromatographed over neutral alumina (activity grade 1). Elution of the column with benzene afforded additional solid product, crystallization of which from ether–hexane (2:1) gave 407 mg of a white crystalline compound, **16**, mp 121.5–122.5°; ν_{max} 1745 (ester) and 1709 cm^{-1} (ketone); τ 8.82 (3 H singlet, $>CCH_3$), 8.53 (3 H singlet, $>C(CH_3)CO_2CH_3$), 6.35 (3 H singlet, $COOCH_3$), 6.08 (4 H singlet, OCH_2CH_2O), and 4.58 (1 H triplet, vinyl hydrogen).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.16; H, 7.59.

Method B.[23c] To a magnetically stirred suspension of potassium *t*-butoxide (7.5 g) in dry benzene (300 ml) was added, under nitrogen, a solution of the ketal (17 g) in dry benzene (50 ml) during 15 min. After warming the reaction mixture at 58° for 20 min, most of the solvent was removed by distillation under nitrogen. Dry benzene (200 ml) was introduced and again distilled off, the process being repeated twice. Dry benzene (200 ml) was added and the dark red solution cooled to 5° by an ice bath. A solution of methyl iodide (60 ml) in dry benzene (60 ml) was added dropwise and the mixture stirred at ice bath temperature for 1 hr and then refluxed for 14 hr. More methyl iodide (40 ml) in dry benzene (40 ml) was introduced and reflux continued for an additional 8 hr. The cooled reaction mixture was washed with brine twice and dried (Na_2SO_4). Removal of solvent gave a solid which was crystallized from benzene–hexane to give 11 g of the methylated ketal **16**, mp 121–124°.

5α-Carbomethoxy-5β,9α-dimethyl-6α-hydroxy-1-oxo-Δ$^{4(10)}$-octalin (18a). A solution of the hydroxyl ketal **17** (1.625 g) in a mixture of acetone (70 ml) and water (2.5 ml) was treated with *p*-toluenesulfonic acid (0.617 g) in 3.25 ml of 1:1 water–acetone solution. The mixture, after standing at room temperature for 24 hr, was concentrated *in vacuo* and the residual oil treated with ice and extracted with 1:1 methylene chloride–ether mixture. The organic extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure. Crystallization of the residue from ether–hexane gave 1.218 g of needles of the hydroxy ketone, mp 83–84°; ν_{max} 3500 (OH) and 1700 cm^{-1} (broad, >C=O, CO_2CH_3); τ 8.85 (3 H singlet, $>CCH_3$), 8.45 (3 H singlet, $-C(CH_3)CO_2CH_3$), 6.32 (3 H singlet, CO_2CH_3), and 4.0 (broad triplet, >C=CH).

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.54; H, 7.99. Found: C, 66.41; H, 7.78.

6α-Acetoxy-5α-carbomethoxy-5β,9α-dimethyl-1-oxo-Δ$^{4(10)}$-octalin (18b). A solution of the above hydroxy ketone (0.987 g) in a mixture of acetic anhydride (3 ml) and pyridine (4.5 ml) was allowed to stand overnight at room temperature. Usual work-up led to 1.013 g of the crude acetate which was crystallized from ether–hexane to give 1.005 g (87%) of **18b**, mp 104–106°; ν_{max} (Nujol) 1740 (–OAc, CO_2CH_3), 1704 (>C=O); τ 8.89 (3 H singlet, $>CCH_3$), 8.71 (3 H singlet, $C(CH_3)CO_2CH_3$), 8.01 (3 H singlet, $-OCOCH_3$), 6.4 (3 H singlet, CO_2CH_3), 5.56 (1 H quartet, CHOAc), and 4.0 (1 H triplet, J = 4 cps, >C=CH).

Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.45; H, 7.62.

Ethylene Ketal of 5α-Carbomethoxy-5β,9α-dimethyl-6α-hydroxy-1-oxo-Δ$^{4(10)}$-octalin (17). Method A. An ice-cold solution of 2.87 g of the ethylene ketal **16** in 150 ml of dry methanol was treated dropwise with a solution of 1.45 g of sodium borohydride in 50 ml of methanol and then allowed to stand at room temperature for 18 hr. The reaction was worked up as in the previous sodium borohydride reduction. Evaporation of the solvent gave 1.87 g of white crystalline alcohol **17**, mp 90–91°; ν_{max} 3535 (OH), 1710 (CO_2CH_3), and 1660 cm^{-1} (weak C=C); τ 8.93 (3 H singlet, $>CCH_3$), 8.45 (3 H singlet, $-C(CH_3)CO_2CH_3$), 6.32 (3 H singlet, CO_2CH_3), 6.04 (4 H singlet, OCH_2CH_2O), and 4.17 (1 H triplet, >C=CH–, J = 4 cps).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 65.11; H, 8.37.

Method B. An ice-cold solution of 17.4 g of the ethylene ketal **16** in a mixture of methanol (250 ml) and water (20 ml) was treated portionwise with sodium borohydride (2.94 g) during 1 hr. The mixture was stirred at 5–10° for 3 hr. Most of the solvent was evaporated under reduced pressure, and the oily residue was treated with ice, extracted thrice with ether (three 125-ml portions), washed with brine, and dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue from hexane containing a trace of ether gave large prisms of the alcohol **17**, 16.092 g, mp 87–89.5°.

Ethylene Ketal of 5α-Carbomethoxy-6α-hydroxy-5β,9α-dimethyl-1-oxo-*trans*-decalin (19). A solution of 1.97 g of the above alcohol in 100 ml of ethanol or methanol was hydrogenated over 1.52 g of 10% palladium on charcoal[21] at atmospheric pressure for 7 days. When the catalyst was collected and the solution extracted with hot methylene chloride 1.49 g of oil was obtained which quickly solidified to give the solid decalin **16**, mp 95–122°. Repeated crystallization from ether gave 649 mg of crystalline compound, mp 132–134°; ν_{max} 3610 (OH) and 1715 cm^{-1} (ester); τ 9.12 (CCH_3), 8.66 (CCH_3), and 6.13 (ketal).

Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.40; H, 8.78. Found: C, 64.30; H, 8.71.

A careful tlc examination of the mother liquor (silica gel, ether–hexane 3:1) revealed that the mixture was composed predominantly of the desired *trans*-2-decalol and three other components possessing close R_f values.

Ethylene Ketal of 6α-Hydroxy-5α-hydroxymethyl-5β,9α-dimethyl-1-oxo-*trans*-decalin (20). A solution of 1.06 g of ethylene ketal **19** in 50 ml of dry tetrahydrofuran was added slowly to an ice-cold slurry of 502 mg of lithium aluminum hydride in 40 ml of dry ether. The stirred reaction mixture was allowed to come to room temperature, stirred overnight, and then refluxed for 30 min the next morning. The excess lithium aluminum hydride was decomposed with a saturated sodium potassium tartrate solution while stirring for 10 min. The clear ether solution was decanted and washed twice with saturated sodium chloride solution. The ether was evaporated *in vacuo* leaving an oil that solidified from ether–hexane (2:1) (753 mg), mp 129–131°; recrystallization from ether–hexane yielded white crystals, mp 136.5–137°; ν_{max} 3330 cm^{-1}; τ 8.99 (3 H singlet, CCH_3), 8.75 (3 H singlet), and 6.08 (4 H singlet, OCH_2CH_2O).

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.35; H, 9.63.

The diacetate derivative of the above diol was prepared by treating **20** with a mixture of 20 ml of acetic anhydride and 20 ml of pyridine at room temperature for 18 hr. The reaction mixture was evaporated to dryness *in vacuo* and flashed several times with benzene. The crude dark oil (1.04 g) was chromatographed in benzene over 50 g of neutral grade 2 alumina (Woelm). Elution of the column with benzene gave 876 mg of oil that solidified on trituration with ether–hexane (1:1). Recrystallization from hexane gave 584 mg of the crystalline diacetate **21**, mp 117–118°; ν_{max} 1745, 1738, 1250, and 1235 cm^{-1} (acetates); τ 8.98 (3 H singlet, $>CCH_3$), 8.90 (3 H singlet, $>C(CH_3)CH_2OAc$), 7.95 and 7.93 (6 H, each singlet (2OAc), multiplet at 6.05 (4 H, $-OCH_2CH_2O$, 2 H quartet, $-CH_AH_BOAc$), τ_A 5.38, τ_B 5.89 (J_{AB} = 12 cps), and 5.37 (triplet, $-CHOAc$).

Anal. Calcd for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53. Found: C, 64.83; H, 8.52.

In another experiment the crude diol resulting from the lithium aluminum hydride reduction of 7.5 g of the ethylene ketal **19** was directly acetylated with 50 ml of pyridine and 20 ml of acetic anhydride. After remaining overnight at room temperature the mixture was taken to dryness *in vacuo* and the last traces of acetic anhydride were removed by flashing off with benzene. The oily residue was dissolved in ether, the solution filtered from a small amount of suspended material, and the filtrate diluted with *n*-pentane. The crystals that separated on cooling were collected and dried to give 8.3516 g of the ketal diacetate, mp 118–119°.

6α-Acetoxy-5α-acetoxymethyl-5β,9α-dimethyl-1-oxo-*trans*-decalin (22). A solution of the ketal diacetate **21** (1.03 g) in a mixture of acetone (25 ml) and water (7 ml) was treated with *p*-toluenesulfonic acid (700 mg) and the mixture allowed to stand at room temperature for 48 hr. Most of the solvent was removed *in vacuo* and the residue treated with water and extracted with ether (four 20-ml portions). The ether extract was washed once with cold aqueous

potassium bicarbonate and twice with brine and dried (Na_2SO_4). Removal of solvent gave an oily residue which was a mixture of three compounds (tlc, alumina, $CHCl_3$–hexane, 5:1). The mixture was chromatographed over neutral alumina (activity 2, 43 g) and eluted with chloroform–hexane (5:1). Evaporation of the first 40 ml of eluate gave fairly pure **22**. Fractions 3–8 (10 ml each) were combined and evaporated, and the residue was crystallized from ether to give a monoacetate, mp 135–137°; ν_{max} 3500, 1725 (OAc), and 1702 (C=O) cm^{-1}; τ 8.86 (6 H singlet), 7.86 (3 H singlet), and 5.65 (2 H singlet, broad).

Fractions 14–20 (each 15 ml, eluted with 1% $CHCl_3$–MeOH) were combined and evaporated to give the diol **23** (28 mg) which was crystallized from ether, mp 122–124°; ν_{max} 3350 and 1704 cm^{-1}. The monoacetate, the diol **23**, and the diacetate **22** were combined and acetylated with acetic anhydride (4 ml) and pyridine (6.5 ml). The product, worked up as indicated elsewhere, was crystallized from ether–pentane to give the diacetate **22**, 0.645 g (70%), mp 112–114°. Recrystallization from ether–*n*-hexane (1:1) gave an analytical sample: mp 113–114°; ν_{max} 1745, 1715, and 1235 cm^{-1}; τ 8.98 (3 H singlet, $\geqslant CCH_3$), 8.82 (3 H singlet, $\geqslant C(CH_3)CH_2OAc$), 7.98 (3 H singlet, $-OCOCH_3$), 7.95 (3 H singlet, $-OCOCH_3$), and 5.65 (2 H broad singlet, CH_2OAc).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.80; H, 8.33.

The yield was improved to 81% when deketalization was done in 2-g batches (24 hr instead of 48 hr at room temperature), acetylating the crude product and crystallizing the resulting diacetate from ethyl acetate–pentane. Chromatography of the mother liquor over silicic acid and elution with ether–hexane (3:1) provided an additional 0.634 g (11%) of the keto diacetate **22**, mp 110–113°, bringing the total yield to 92%.

Ethylene Ketal for 6α-Acetoxy-5α-acetoxymethyl-5β,9α-dimethyl-1-oxo-$\Delta^{4(10)}$-octaline (29). To a magnetically stirred suspension of lithium aluminum hydride (5 g) in dry ether (200 ml) was added dropwise at room temperature a solution of **17** (11 g) in ether (130 ml). The mixture was stirred at room temperature for 24 hr and then gently refluxed for 1 hr. It was then cooled in an ice bath and decomposed with a saturated solution of sodium sulfate and sodium potassium tartrate and the product worked up as indicated elsewhere. The crude, colorless oil was treated with acetic anhydride (20 ml) and pyridine (20 ml) and left overnight at room temperature. Work-up in the usual manner led to the ketal diacetate **29** as a heavy oil (15.5 g) which was used as such for the next reaction. An analytical sample, purified by preparative tlc and sublimation under high vacuum, melted at 95–97°; ν_{max} (Nujol) 1745 (OAc), 1720 (OAc), and 1245 ($OCOCH_3$) cm^{-1}; τ 4.47 (1 H triplet, vinyl), 5.42 (1 H multiplet, $CHOAc$), 5.85 (2 H singlet, CH_2OAc), 6.09 (4 H singlet, OCH_2CH_2O), 8.0 (3 H singlet, $-OCOCH_3$), 8.05 (3 H singlet, $OCOCH_3$), 8.79 (3 H singlet, $\geqslant C(CH_3)CH_2OAc$), and 8.90 (3 H singlet, $\geqslant CCH_3$).

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.81; H, 8.07.

5α-Acetoxymethyl-6α-acetoxy-5β,9α-dimethyl-1-oxo-$\Delta^{4(10)}$-octalin (30). To a solution of the above crude ketal (15.4 g) in acetone (200 ml) was added a solution of *p*-toluenesulfonic acid (6.5 g) in a mixture of water (50 ml) and acetone (50 ml). The mixture, after standing at room temperature for 23 hr, was concentrated under reduced pressure, cooled, treated with ice, and extracted with ether (four 100-ml portions); the ether extract was washed with brine and dried (Na_2SO_4). Removal of solvent gave an oil (13.5 g) which was treated with acetic anhydride (15 ml) and pyridine (10 ml). Usual work-up afforded, after overnight drying *in vacuo*, the crude ketone **30** as a pale yellow oil (13 g).

6α-Acetoxy-5α-acetoxymethyl-5β,9α-dimethyl-1-oxo-*trans*-decalin (22). A solution of the above crude diacetoxy ketone **30** (13 g) in glacial acetic acid (200 ml) was reduced with platinum oxide (2 g) at 19 psi for 2 hr at room temperature. The mixture was filtered and the catalyst washed with glacial acetic acid (two 25-ml portions). The solvent from the combined filtrates was evaporated under reduced pressure to give 13 g of an oil which was dissolved in acetone (200 ml) and oxidized with the Jones' reagent at 0°. After stirring the mixture at 0° for 0.5 hr, excess of the oxidant was destroyed by dropwise addition of 2-propanol. The solution was concentrated to half its volume under reduced pressure and poured onto ice. Extraction into ether, washing with brine, drying over sodium sulfate, and evaporation of the filtered solution gave **22** as an oily solid. Chromatography on silicic acid (150 g), elution with benzene (500 ml), and evaporation of the eluate gave 1.5 g of a yellow oil which was not investigated. Continued elution with ether–benzene (1:1; l.) and evaporation yielded a colorless oil. Crystallization from benzene–hexane gave 7.603 g of the ketone **22**, mp 105–112°. Recrystallization from the same solvent pair raised the melting point to 111–113°. This sample was indistinguishable from **22** (melting point, mixture melting point, ir) obtained by Pd–C hydrogenation of **17**.

6α-Hydroxy-5α-hydroxymethyl-5β,9α-dimethyl-1-oxo-*trans*-decalin (23). A. By Deketalization of 20. A solution of **20** (170 mg) in a mixture of acetone (7 ml) and water (3 ml) was treated with *p*-toluenesulfonic acid (70 mg) and the mixture allowed to stand at room temperature for 24 hr. The bulk of the solvent was removed under reduced pressure; the residue was treated with ice, extracted with ether (five 5-ml portions), washed with brine, and dried (Na_2SO_4). Removal of solvent gave a white solid (104 mg). Two crystallizations from $CHCl_3$–hexane gave the analytical sample, mp 121–123°; ν_{max} 3300 (OH) and 1706 (C=O) cm^{-1}.

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.17; H, 9.62.

B. By Alkaline Hydrolysis of 22. A solution of the keto diacetate **22** (200 mg) in methanol (5 ml) was treated with a solution of potassium hydroxide (200 mg) in water (2 ml) and the mixture refluxed under a nitrogen atmosphere for 1 hr. Most of the solvent was then removed under reduced pressure; the residue was treated with ice, extracted with chloroform (four 10-ml portions), washed with brine, and dried (Na_2SO_4). Removal of solvent gave an oil which rapidly solidified on trituration with ether. Two crystallizations from $CHCl_3$–hexane gave the diol identical with the sample prepared as above.

5β,9α-Dimethyl-1,6-dioxo-*trans*-decalin (25). The diol **23** obtained in the above experiment was dissolved in acetone (15 ml) and oxidized with the Jones' reagent[25] at room temperature. After stirring for 1.5 hr, the excess of oxidant was destroyed with 2-propanol; the mixture was concentrated *in vacuo*, treated with ice, and extracted with ether. The ether extract was washed with aqueous 5% sodium hydroxide solution (five 4-ml portions) and the alkaline extract back-washed with ether once. Acidification of the cold alkaline solution with cold concentrated hydrochloric acid followed by ether extraction (four 20-ml portions), washing with brine, drying over Na_2SO_4, and evaporation of the filtered solution gave the acid as a brown gum (66 mg). This was dissolved in a mixture of glacial acetic acid (10 ml) and concentrated hydrochloric acid (3 ml) and the resulting yellow solution refluxed under nitrogen for 2 hr. The cooled solution was then concentrated under reduced pressure; the residue was treated with ice and extracted with ether. The ether extract was washed with aqueous 5% sodium hydroxide solution to remove any undecarboxylated acid, then with brine, and dried (Na_2SO_4). Removal of solvent gave a yellow solid which was purified by chromatography on silicic acid (3 g) and eluted with ether–hexane (1:1). Evaporation of the first 25 ml of the eluate gave a white solid which on crystallization from pentane and ether afforded the diketone **25**, 26.5 mg, mp 77–90°; ν_{max} (Nujol) 1702 cm^{-1} (broad, >C=O); τ 8.99 (doublet, J = 6.5 cps, $-CHCH_3$) and 8.62 (singlet, $\geqslant CCH_3$).

5β,9α-Dimethyl-1,6-dioxo-*trans*-decalin. Liquid ammonia (10 ml; dried over sodium) was distilled into a solution of 5β,9α-dimethyl-1,6-dioxo-$\Delta^{5(10)}$-octalin[13] (**26**) (140 mg) in dry tetrahydrofuran kept at −70°. Lithium (60 mg) cut into small pieces was added and the mixture stirred for 15 min. Ethanol was run into the rapidly stirred mixture to decolorize the blue color. After evaporation of ammonia, water was added and the diol extracted with ether (four 10-ml portions), washed with brine, and dried (Na_2SO_4). Removal of the solvent gave a pale pink gum, **27** (devoid of ir bands due to the keto groups), which without purification was oxidized at 0° with the Jones' reagent.[25] Usual work-up led to a yellow solid which was purified by chromatography on silicic acid and elution with ether–hexane (1:1). Evaporation of first 15 ml of the eluate, followed by crystallization of the residue, gave the dimethyldecalin **25**, mp 74–77°. The melting point remained undepressed on admixture with **25** and the respective infrared spectra were identical.

Ethynylation[28,29] of 6α-Acetoxy-5α-acetoxymethyl-5β,9α-dimethyl-1-oxo-*trans*-decalin (22). A solution of 156 mg of ethoxyacetylene–hexane (50%) was treated with 138 mg of butyllithium–hexane (15%) in a nitrogen atmosphere for 10 min at −25°. The keto diacetate **22** (224 mg) in 10 ml of dry ether was added slowly to the cold mixture and the mixture allowed to stand for 1 hr at −25°. After standing 3 hr at room temperature, the reaction was poured into 10 ml of water, and the ethereal layer was separated and washed with water. The oily product showed the expected maxima in the infrared spectrum for the ethynylcarbinol **32**: ν_{max} (CCl_4) 3560 (OH), 2268 (C≡C), 1742 and 1235 cm^{-1} (acetate).

The acetylide was then immediately treated with 1 ml of 10% sulfuric acid in 10 ml of ethanol and allowed to stand overnight. The solution was concentrated *in vacuo* and diluted with benzene. The benzene solution was extracted with 10% sodium bicarbonate solution and dried over anhydrous sodium sulfate. Evaporation of the solvent *in vacuo* gave 231 mg of crude oil. The product was chromatographed in benzene over neutral Woelm alumina (activity grade 2, 10 g). Elution of the column with benzene gave 72.4 mg of oil (one spot on tlc). Elution with ether–hexane gave 11.3 mg more of the above compound **33**: ν_{max} ($CHCl_3$) 1748, 1724, 1642, and 1235 cm^{-1}; the nmr spectrum contained, besides the usual signals due to methyls and acetates, a low-field proton at τ 4.67 ascribable to the hydrogen α to the ester group.

A second compound was obtained (31.1 mg) by elution of the column with 150 ml of ether: ν_{max} ($CHCl_3$) 3534 (OH), 1750–1700, and 1235 cm^{-1} (broad).

A third compound was eluted with methanol–ether (1:1, 200 ml): ν_{max} ($CHCl_3$) 3675 (OH), 1705 (unsaturated ester), and 1630 cm^{-1} (C=C), no acetate absorption. Treatment of this compound (56.4 mg) with acetic anhydride and pyridine in the usual manner gave a crude oil. The acetate derivative proved to have an infrared spectrum identical with that of the first compound eluted from the column (**33**).

A solution of the above ester **33** (79 mg) in glacial acetic acid (5 ml) was refluxed 4 hr with 27 mg of freshly sublimed selenium dioxide. The acetic acid was removed *in vacuo* leaving 74 mg of darkly colored oil; chromatography over 5 g of activity grade 3 neutral alumina and elution with benzene yielded 51 mg of a pure solid compound, **34**, mp 144–145°; ν_{max} (KBr) 1760 (lactone), 1740 (acetate), 1640 (C=C), and 1240 cm^{-1} (acetate). The infrared (CCl_4) and mass spectra and mobilities on tlc were identical with those of an authentic sample obtained by the degradation of andrographolide.

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A General Method for Synthesizing Optically Active 1,3-Disubstituted Allene Hydrocarbons[1,2]

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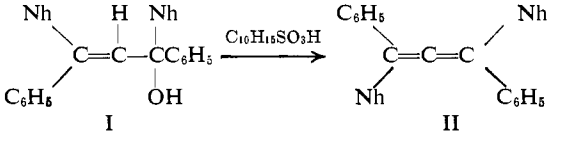
Abstract: Optically active 1,3-diphenylallene, $[\alpha]^{25}D$ +459°, 5,6-nonadiene, $[\alpha]^{28}D$ −7.5°, 3,4-heptadiene, $[\alpha]^{25}D$ +11.2°, and 2,3-pentadiene, $[\alpha]^{25}D$ −25.3°, have each been prepared in high yield from the corresponding ethyl N-nitroso-N-(*trans*-2,3-disubstituted cyclopropyl)carbamates *via* the corresponding diazocyclopropanes. The nitrosocarbamates were prepared from the *trans*-2,3-disubstituted cyclopropanecarboxylic acids which were resolved using standard bases. This method appears to be the first general route into optically active 1,3-disubstituted allene hydrocarbons. Routes through other diazocyclopropane precursors were shown to be lower yield processes.

Although molecular dissymmetry, and hence potential optical activity, in allenes was recognized as early as 1875,[4] they have been found to be surprisingly difficult to synthesize.[5] This has been especially true in the case of allene hydrocarbons (in which the molecule contains no resolving "handle"). In fact, although isolated cases have appeared, no general method for their preparation has been reported to date.

The first resolution of an active allene hydrocarbon involved the asymmetric synthesis of (+)- and (−)-1,3-diphenyl-1,3-di-α-naphthylallene (II) from the tetraarylallyl alcohol I using *d*-camphorsulfonic acid as the dehydrating agent.[6] The resulting allene was reported as being "feebly dextrorotatory." That this represented



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low optical purity was demonstrated by simple recrystallization to give the allene of high optical rotation, $[\alpha]^{17}_{5641}$ +437°. An attempted generalization of this method (replacement of one naphthyl by tolyl or pentadeuteriophenyl) was not successful.[7]

A particularly ingenious synthesis of optically active allene hydrocarbons is that of Jacobs, in which two active 1,3-diarylallenes, IV, were obtained by chromatographing inactive 1,3-diarylpropynes, III, on a column

(1) Based upon dissertations submitted by J. M. Walbrick and J. W. Wilson, Jr., to the Faculty of the University of Florida in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) A preliminary account of this work has been presented: W. M. Jones, J. W. Wilson, Jr., and F. B. Tutwiler, *J. Am. Chem. Soc.*, 85, 3309 (1963).

(3) Alfred P. Sloan Fellow, 1963–1967.

(4) For a comprehensive review of the chemistry of allenes, see H. Fischer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 13.

(5) For reports in the literature before 1930 of unsuccessful attempts to prepare optically active allenes, see K. Zeigler and W. Sauermilch, *Chem. Ber.*, **63**, 1851 (1930); A. Lapworth and E. Wechsler, *J. Chem. Soc.*, 38 (1910); O. Dimroth and H. Feuchter, *Chem. Ber.*, **36**, 2238 (1903); C. D. Hurd and C. N. Webb, *J. Am. Chem. Soc.*, **49**, 546 (1927). For examples of resolutions of allenes containing resolving groups, see E. P. Kohler, J. T. Walker, and M. Tishler, *ibid.*, **57**, 1743 (1935); E. P. Kohler and W. J. Whitcher, *ibid.*, **62**, 1489 (1940); J. H. Wotiz and R. J. Palchak, *ibid.*, **57**, 2619 (1935).

(6) P. Maitland and W. H. Mills, *J. Chem. Soc.*, 987 (1936).

(7) G. R. Clemo, R. Raper, and A. C. Robson, *ibid.*, 431 (1939).